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JAPANESE MEDICAL MATERIEL

TETRADOTOXIN

(Injection of Neurotoxin of Tetrads)

REPORT NO. 249

25 July 1946

MEDICAL ANALYSIS SECTION
5250th Technical Intelligence Company
APO 500

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TETRADOTOXIN

(Injection of Neurotoxin of Tetradons)

SOURCE: Tokyo, Japan.

IMPORTANCE: Not previously reported. A neurotoxin extracted from tetradons. No identical product is recorded in available standard American references.

DESCRIPTION: Twelve amber glass ampuls, each containing 1 cc. of tetradotoxin, are packaged twelve per cardboard container. The solution in each ampul is slightly yellowish and contains a fine sediment, probably the result of decomposition.

SUMMARY OF GENERAL INFORMATION: Tetradotoxin is a neurotoxin extracted from tetradons and its action is due to its irritation of both the peripheral and central nervous systems. Its degree of action is claimed to be directly related to the dosage. Small doses paralyze the sensory nerves, motor nerves and the central spasm center. Larger doses cause paralysis of the vagus. Large doses paralyze the motor nerves of the blood vessels, the diaphragm and finally result in death from respiratory paralysis. Adequate therapeutic dosage consists of employing an amount sufficient to attain sensory and motor paralysis but to avoid respiratory paralysis.

Tetradotoxin is claimed to possess anodyne, antispasmodic and sedative properties. It is as powerful in action as curare, slower than morphine but more lasting (12 to 20 hours) than the latter. The average therapeutic dose is 1 cc., injected subcutaneously, and this is 1/14 of the minimum lethal dose for humans. Standardization of the product is made by determining the minimum lethal dose per kilogram of body weight for marmots. One-fourteenth of this MLD is then diluted fifty times, 0.5% phenol is added, and 1 cc. volumes are ampuled.

The literature accompanying the product has been translated and embodied in this report. It describes the physiological action of tetradotoxin, its indications, contra-indications, directions and dosage (including alternative dosage tables), cautions, storage, packaging and manufacturer.

No information is furnished on the chemical nature of the neurotoxin. Results of detailed comparative tests with other drugs possessing all or part of the neurotoxin's properties are not given. The source of this drug is novel.

PHOTOGRAPHS:

Figure 1 - Closed package of Tetradotoxin

Figure 2 - Open package of Tetradotoxin

Figure 3 - Tetradotoxin literature



テトロドトキシン

テトロドトキシンは前内務省東京衛生試験所長兼博士田原良満先生の發見に係る河豚毒素の純正品として、現に醫藥上に供用されつゝある市販品は田原博士發見の下にモルモット體重一キログラムに對する最小致死量の十四分の一に相當する分量を五十倍（人の平均體重を五十キログラムと見做し）したるものを〇・五%石炭酸水一cc中に含せしめたる一回の注射量（人の致死量の十四分の一）として朝子蟻球に入れ液兩中に抽出されたるものなり。

テトロドトキシンの生理的作用

テトロドトキシンは末梢及中枢神経に影響する一種の神經毒にして少量なる場合には先づ知覚神経を麻痺し、次で運動神経及痙攣中樞を麻痺せしめ、これより稍々多量なるものは生命活動を麻痺してこれが鎮静作用を達し、甚重しき場合には遂に血管運動神経及微循環を時時中絶せしめ遂に死に至るものなり。之が過量（可及及過量）を麻痺せしめし時中絶を度とする程度）を適用すれば鎮痛、鎮靜、鎮痙攣としてモルモット及其他の麻酔劑の及び得ざる作用を補充し得ると共にクラーレの效用を兼ね而も忌むべき副作用もほとんどなきを經驗する動物試験及多數の臨床實驗により認められたるものにして治癒し難き病に適用推察せられつゝあり。

テトロドトキシンの適應症

- 一、鎮痛劑として痛性神經痛、一般痛、筋肉及關節ロイマチス、創傷、火傷、打撲傷、挫傷、肩膊等に因する疼痛に顯著の鎮痛作用を發揮し殊に神經痛、筋肉及關節ロイマチスは本劑の適用によつて顯著ならざる限り全治を來す。
- 二、痙攣鎮靜の目的にて冬季長骨痙攣症、瘧疾、ウキタル苔疹、ストロフルス、疥癬、頭癬、皮膚炎等に應用すれば痙攣を緩解し其を鎮靜を起す。
- 三、呼吸鎮靜劑として喘息、百日咳等に應用。
- 四、鎮痙攣劑として月經痛及其他の痙攣を緩解し、殊に破傷風の痙攣には特效藥とまで稱せらる。
- 五、充血作用の上よりして陰萎及婦人の分娩後血瘀症に對しヨヒムビンの效なき場合にも奏效せり。
- 六、尿意鎮靜作用の上より夜尿症に應用し早效あり。

以上列載せる適應症は既に實驗せられたる多數醫家の報告に基きたるものにして今後益々本劑の適應症は擴大せらるゝと見る傾向を有す。（實驗報告書より即入用の前に御中

テトロドトキシンの禁忌症

今日までの實驗を綜合するに本劑を反覆使用すれば肺性血腫に充血を來し初めは往々前點近傍に限局し、更に反覆すれば肺底肺縁處に達し肺血を來し、同時に尿道も充血するよりして膀胱若くは尿道疾患あるものに對して其副作用は甚大なり。

テトロドトキシンの用法用量

本劑は普通市販品一朝子管の内容即ち一ccを一回の用量とするも患者の體質、年齢、體重、病状等により調節するを要す必要あれば注意しつゝ漸次増量し一回二・〇ccに至るを得べし。其應用の方式は主として皮下に注射するものにして毎日一回或は隔日に一回宛注射を行ふべく其例を左の如し（大人量を云ふ）。

第一法		第二法		第三法		第四法	
一日	〇・五 cc	一日	〇・五 cc	一日	一・〇 cc	一日	一・〇 cc
二日	〇・六 cc	二日	一・〇 cc	三日	一・〇 cc	二日	一・〇 cc
三日	〇・七 cc	三日	〇・六 cc	五日	一・〇 cc	三日	一・〇 cc
四日	〇・八 cc	四日	一・〇 cc	七日	一・〇 cc	四日	一・〇 cc
五日	〇・九 cc	五日	〇・七 cc	九日	一・〇 cc	五日	一・〇 cc
六日	一・〇 cc	六日	一・〇 cc	十一日	一・〇 cc	六日	一・〇 cc
七日	一・一 cc	七日	〇・八 cc	十三日	一・〇 cc	七日	一・〇 cc
八日	一・二 cc	八日	一・〇 cc	十五日	一・〇 cc	八日	一・〇 cc
九日	一・三 cc	九日	〇・九 cc	十七日	一・〇 cc	九日	一・〇 cc
十日	一・四 cc	十日	一・〇 cc	十九日	一・〇 cc	十日	一・〇 cc

注射部位 上膊若くは肩間部の皮下を選び右の如く消毒法を施し、滅菌したる注射器にテトロドトキシンを吸引して正に注射する可き、又上腕、臀部、腹部心窩部等疾病の局部に近接する部分を選ばざる要なきも大なる静脈を傷むる虞に注意すること所要なり。而して本劑注射後其力の現はるゝ時間はモルヒネに比し遙きも持続の時間はモルヒネより抑へ長く十二時間乃至三十時間以上達するに達せらるゝ。又本劑を用法の下に應用すれば常時作用は強きも多量の蓄積性は乏を來するものゝ如し、本劑注射後往々一過性の口舌生炎の如き異常、頭部充血、頭痛等を感ずる者あり。但し此作用は個人の感受性による傾向あること勿論なり、されど忌むべき副作用にはあらざるを以て安心して使用して可なり。

貯藏法 本劑は避光に列して貯ふ。

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(C. L. D. M. D. C.)

Translation of Accompanying Literature

TETRADOTOXIN

Tetradotoxin is the toxins of tetrads discovered by Yoshizumi Tahara, Doctor of Pharmacology and formerly Chief of the Tokyo Sanitary Research Laboratory attached to the Home Office. The product now being used in medical treatment is manufactured under the supervision of Doctor Tahara. The quantity equivalent to 1/14 of the minimum lethal dose per kilogram body weight of a marmot is diluted fifty times (assuming the average body weight of humans to be 50 Kg.) and is enclosed in 1 cc. ampules containing 0.5% phenol and sterilized. The contents of one ampule constitute one dose (1/14 of lethal dose of humans).

PHYSIOLOGICAL ACTION OF TETRADOTOXIN: Tetradotoxin is one type of poison to the nerves causing an irritation of both the peripheral nervous system and the central nerves. In small dosages, first, it paralyzes the sensory nerves, next the motor nerves and finally the central spasm center. In slightly larger doses it paralyzes the vagus nerve and intercepts the inhibitory action. In large dosages it paralyzes the motor nerves of the blood vessels, the diaphragm and the respiratory center finally causing death. However, if a proper dose is administered (the amount that paralyzes the sensory and motor nerves but not the respiratory center) it displays an action that morphine and other anesthetics do not attain - that is, an anodyne, antispasmodic and sedative action - and in addition it is as powerful as curare. Moreover, it has been proven by numerous clinical experiments and precise animal tests that it does not cause any secondary reactions. It is being applied and recommended in various medical treatments.

INDICATIONS:

1. As an anodyne it is markedly effective against pain caused by leprous neuralgia, general neuralgia, rheumatism of the muscles and joints, cuts, burns, bruises, stiff shoulders, etc. It completely cures neuralgia and rheumatism of the muscles and joints except in chronic cases.
2. As an antipruritic it relieves and speeds the recovery from skin itch in winter, pruritis, Vidal's disease, strophulus, scabies, ringworm and dermatitis.
3. As a respiratory sedative it may be applied in asthma and whooping cough.
4. As an antispasmodic it may be applied in stomach and other spasms. It is especially effective in spasms in tetany.

5. It has a blood congesting action and is even effective where Yohimbine is not in impotence and female apathy,

6. As a urinary sedative it is effective in enuresis.

The above mentioned indications are listed based on the reports of many clinical doctors and there is a tendency which indicates that the scope of medical treatment will be greatly enlarged hereafter,

CONTRA-INDICATIONS: Records of experiments to date show that repeated use of this drug causes congestion of the mucous membrane of the bladder. At first, this congestion is limited to the apex but repeated use causes a marked congestion of the whole mucous membrane of the bladder as well as the urethra. Consequently, this drug must not be used in cases of irritations of the bladder or the urethra.

DIRECTIONS AND DOSAGES: The contents of one ampule, that is 1 cc., constitutes an average dose but this should be adjusted in accordance with physical condition, age and weight of the patient and conditions of the disease (if necessary it may gradually be increased with caution up to 3 cc.). Usually injection is by the hypodermic route once a day or on alternate days shown as follows (adult dose),

1st Method

1st day - 0.5 cc.
2nd day - 0.6 cc.
3rd day - 0.7 cc.
4th day - 0.8 cc.
5th day - 0.9 cc.
6th day - 1.0 cc.
7th day - 1.1 cc.
8th day - 1.2 cc.
9th day - 1.3 cc.
10th day - 1.4 cc.

2nd Method

1st day - 0.5 cc.
2nd day - 1.0 cc.
3rd day - 0.6 cc.
4th day - 1.0 cc.
5th day - 0.7 cc.
6th day - 1.0 cc.
7th day - 0.8 cc.
8th day - 1.0 cc.
9th day - 0.9 cc.
10th day - 1.0 cc.

3rd Method

1st day - 1.0 cc.
3rd day - 1.0 cc.
5th day - 1.0 cc.
7th day - 1.0 cc.
9th day - 1.0 cc.
11th day - 1.0 cc.
13th day - 1.0 cc.
15th day - 1.0 cc.
17th day - 1.0 cc.
19th day - 1.0 cc.

4th Method

1st day - 1.0 cc.
2nd day - 1.0 cc.
3rd day - 1.0 cc.
4th day - 1.0 cc.
5th day - 1.0 cc.
6th day - 1.0 cc.
7th day - 1.0 cc.
8th day - 1.0 cc.
9th day - 1.0 cc.
10th day - 1.0 cc.

CAUTIONS: It is best to inject tetradotoxin subcutaneously on the upper arm or shoulder after the usual precautions. Draw the tetradotoxin into a sterilized syringe and inject immediately. Although it may be injected into the upper thigh, hip, the pit of the stomach, or parts adjacent to a focal infection, great care should be taken so as not to injure any large veins. It is slower in action than morphine but its effect is more lasting - twelve to twenty hours. Even if used in regular quantities it does not cause any cumulative action but it seems to be slightly habit forming. In some patients it causes an acute abnormal sensation of the mouth and tip of the tongue, head congestion, headache, etc., but it must be understood that the above reactions vary with the individual's idiosyncrasies. However, as these are not secondary reactions, medication may be continued without fear.

STORAGE: Store with the same cautions as any poisonous drug.

PACKAGING:

1 cc. - 6 ampules
1 cc. - 12 ampules

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